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RESEARCH ARTICLE

Serum neurofilament light chain and cognition decline in US elderly: A cross-sectional study

Xiaodong Liu[1], Jun Chen[1], Chen Meng[2], Lan Zhou[1] & Yong Liu[1]

[1]Department of Neurology, Taihe Hospital, Hubei University of Medicine, Shiyan, China
[2]Department of Anesthesiology, Taihe Hospital, Hubei University of Medicine, Shiyan, Hubei, China

Correspondence
Xiaodong Liu, Department of Neurology, Taihe Hospital, Hubei University of Medicine, Shiyan, China. Tel: +86 0719 8801932; Fax: +86 0719 8801931; E-mail: liuxiaodong@whu.edu.cn

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Abstract

Objective: Early identification of cognitive impairment in neurodegenerative diseases like Alzheimer's disease (AD) is crucial. Neurofilament, a potential biomarker for neurological disorders, has gained attention. Our study aims to investigate the relationship between serum neurofilament light (sNfL) levels and cognitive function in elderly individuals in the United States. **Methods**: This cross-sectional study analyzed data from participants aged 60 and above in the National Health and Nutrition Examination Survey (2013–2014). We collected sNfL levels, cognitive function tests, sociodemographic characteristics, comorbidities, and other variables. Weighted multiple linear regression models examined the relationship between ln(sNfL) and cognitive scores. Restricted cubic spline (RCS) visualization explored nonlinear relationships. The stratified analysis examined subgroups' ln(sNfL) and cognitive function association. **Results**: The study included 446 participants (47.73% male). Participants with ln(sNfL) levels between 2.58 and 2.81 pg/mL (second quintile) performed relatively well in cognitive tests. After adjusting for multiple factors, ln(sNfL) levels were negatively correlated with cognitive function, with adjusted β (95% CI) as follows: immediate recall test (IRT): −0.763 (−1.301 to −0.224), delayed recall test (DRT): −0.308 (−0.576 to −0.04), animal fluency test (AFT): −1.616 (−2.639 to −0.594), and digit symbol substitution test (DSST): −2.790 (−4.369 to −1.21). RCS curves showed nonlinear relationships between ln(sNfL) and DRT, AFT, with inflection points around 2.7 pg/mL. The stratified analysis revealed a negative correlation between ln(sNfL) and cognition in specific subgroups with distinct features, with an interaction between diabetes and ln(sNfL). **Interpretation**: Higher sNfL levels are associated with poorer cognitive function in the elderly population of the United States. sNfL shows promise as a potential biomarker for early identification of cognitive decline.

Introduction

It is well-known that aging is a growing problem in the United States.[1] Aging is closely associated with cognitive decline,[2,3] which is the primary manifestation of dementia, especially Alzheimer's disease (AD).[4] From a mechanical perspective, aging leads to cognitive decline through multiple pathways, including neuronal dysfunction, decreased neural regeneration capacity, neuroinflammation within the brain, and alterations in the blood–brain barrier.[5] Furthermore, previous research has also confirmed that age-related cognitive decline is typical among older adult population.[6,7] Moreover, dementia has emerged as a significant health and life threat facing older adults in the United States,[8] bringing severe medical and economic burdens to society.[9] However, it is sometimes challenging to identify cognitive impairment early because its causes are complex.[10–13] Although some protein molecules found in cerebrospinal fluid, such as tau protein and amyloid-β 42 filaments, have been extensively studied as potential biological markers for early diagnosis of AD[14], their screening value in the general population is severely restricted by their intrusiveness and high cost.[15] Therefore, finding more effective

biomarkers is still essential for identifying early cognitive decline.[16]

Neurofilaments (Nfs) are a class of cylindric proteins found in the cytoplasm of neurons and are primarily responsible for preserving the stability of the neuronal structure. Neurofilament light chain (NfL), a subunit of neurofilaments, is widely expressed in nerve axons. The release of NfL dramatically rises when CNS axons are damaged by inflammation, neurodegeneration, trauma, or ischemia.[17,18] Increased levels of NfL (cerebrospinal fluid or blood) have been detected in a variety of neurological diseases, according to previous studies.[19] Given that NfL levels naturally increase with age,[20–22] it raises the question of whether elevated NfL levels in the elderly population remain associated with cognitive decline after adjusting for age. It is worth exploring. While recent research has provided some supportive evidence,[23–26] other investigations have not found a significant correlation between sNfL levels and specific cognitive test scores,[27,28] indicating that further research is needed to clarify this relationship. Moreover, to the best of our knowledge, there is currently a lack of studies examining the correlation between sNfL and cognitive function in a nationwide elderly population in the United States. Therefore, in this cross-sectional study, we aimed to explore the relationship between sNfL and cognitive decline in an older US population (age ≥ 60 years) using National Health and Nutrition Examination Survey (NHANES) data.

Methods

Study population

The NHANES protocols were authorized by the National Center for Health Statistics (NCHS) ethics review board with the written informed permission of every participant. Such analysis employing de-identified data that were not in direct touch with participants was not regarded as a human subjects study. It was not submitted to institutional review board assessment by National Institutes of Health regulation.[29,30] Researchers all over the world can utilize the NHANES database, which is a freely accessible resource. Still, they must guarantee that their research is in the public interest and abide by all applicable rules and regulations before utilizing the information. For more information, see https://www.cdc.gov/nchs/about/policy.htm. This study followed the Guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[31]

NHANES uses a complex, multistage probability sampling design. As a result, there will be disparities in sampling probability among individuals, necessitating the use of sample weights to adjust the sampling results. As the exposure variable we studied was the level of sNfL, it was a component of the survey subsample. Therefore, we used the weights of that subsample for our analysis. For more details on sampling design and weight calculation, please refer to https://www.cdc.gov/nchs/hus/sources-definitions/nhanes.htm.

We employed weighted samples to produce estimates accurately representing the American population, factoring in the design's stratification and clustering.[32] Our data source was NHANES from the 2013–2014 cycle, encompassing information related to the primary study variable, sNfL, and cognitive tests. Additionally, we accessed publicly available data about four cognitive tests conducted on individuals aged 60 years and older, derived from participants recruited from 2013 to 2014.[33] Participants who had not undergone any cognitive testing or those who had but had not fully undergone all four cognitive tests were eliminated ($N = 268$). Then, we excluded those subjects ($N = 1071$) who skipped sNfL testing or did not have results. Furthermore, we removed the data from the analysis with missing covariates ($N = 56$) while accounting for the effects of the model fit adjustment for covariates. Finally, we included 446 individuals in the research (Fig. 1).

Measurement

Measurements of serum neurofilament light chain

Siemens Healthineers utilizes an innovative high-throughput acridine ester (AE) immunoassay, integrated into the Atellica platform, for measuring sNfL in the NHANES database. Information regarding the development and validation of this test kit can be found in previously published literature.[34] This immunoassay is based on direct AE chemiluminescence detection, employing one antibody and solid-phase magnetic bead capture with another antibody. Researchers have established that this assay highly compares to the traditional single-molecule array (Simoa; Quanterix) assay.[34,35] Furthermore, other pertinent research investigations[36–38] have employed it.

First, sNfL antigen-conjugated acridinium-ester (AE)-labeled antibodies are treated with serum samples. The material is mixed with paramagnetic particles (PMP) coated with a capture antibody to create an antigenic complex containing the AE-labeled antibody and PMP. Then, unbound AE-labeled antibodies are isolated and eliminated, and then acids and bases are added to start chemiluminescence and quantify light emission. A completely automated Attelica immunoassay system is used for every phase. On the NHANES website, thorough guides for laboratory procedures are freely available.[32]

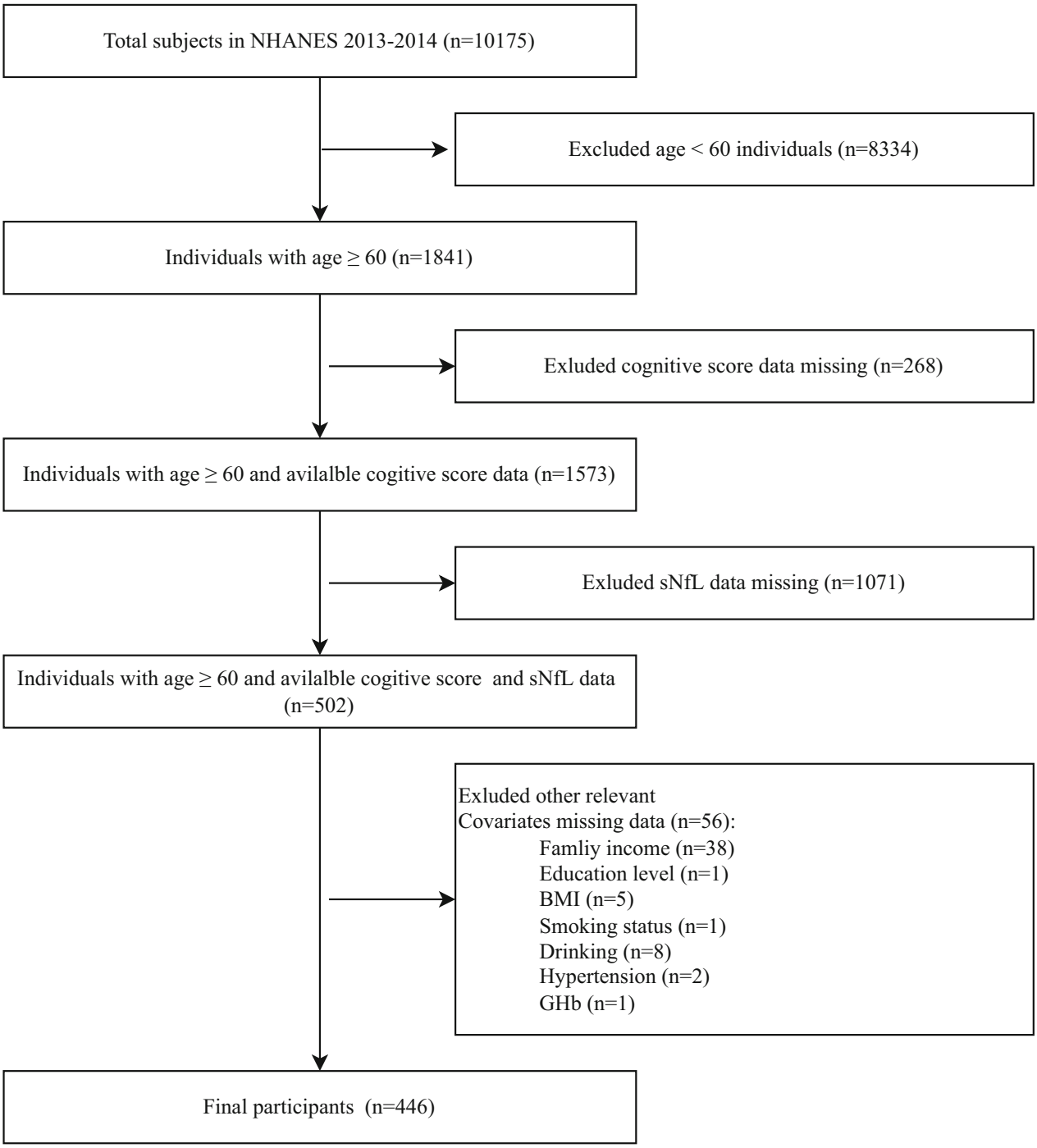

Figure 1. Flow chart of the screening and enrollment of participants. BMI, body mass index, GHb, glycated hemoglobin; NHANES, National Health and Nutrition Examination Survey; sNfL, serum neurofilament light.

Cognitive function assessment

The animal fluency test (AFT), the learning and recall of words from the Creating a Registry for Alzheimer's Disease (CERAD) exam, and the digit symbol substitution test (DSST) were used to measure cognitive performance.[39] Researchers widely use these cognitive tests in cognitive screening and clinical and epidemiologic studies.[40–48] Some research[49–51] on elderly populations has also utilized these four cognitive tests.

Absolute verbal fluency was assessed using the AFT. Each participant was given a minute to respond with as many animals as possible, with each response worth one point.[52] Three consecutive learning trials (immediate recall test, IRT) and one delayed recall (delayed recall test, DRT) comprise the CERAD test. Participants were instructed to remember as many words from the study experiment as possible after studying for the exam. Each trial had a score range of 0 to 10, with 1 point awarded for each accurate response. The IRT is composed of the total scores of these three consecutive learning trials, while the DRT is required after completing the two tests, AFT and DSST (about 8–10 minutes after the start of the word learning trial). The CERAD score is the sum of the four tests.[40] The Digit Symbol Substitution Test (DSST) primarily measures processing speed, sustained attention, and working memory.[53] The task required using a paper table with a key at the top that featured nine numbers and symbols. The 133 boxes next to the numbers had 133 symbols, and participants had 2 minutes to replicate them. The total number of exact matches determines the score. The lower the score on each dimension of cognitive function, the worse the mental process. Besides, according to the NHANES website,[54] the investigator independently scored 10% of the forms a second time and compared and reconciled the two scores as needed.

Covariates

Considering previous references, we gathered sociodemographic information (age, gender, race, education, and family poverty income ratio (PIR)),[55–57] body mass index (BMI),[58] lifestyle (work activity, recreational activity, smoking status, and alcohol consumption status),[59–62] medical history (hypertension, diabetes, stroke, coronary artery disease (CHD), and congestive heart failure (CHF),[63–67] and laboratory data (total cholesterol (TC), high-density lipoprotein (HDL), and glycated hemoglobin (GHb))[68,69] related to the cognitive function or sNfL as confounding variables. Another study on factors influencing sNfL levels within the NHANES database confirmed that the mentioned variables affect sNfL.[36] NHANES responses to survey questions about race and Hispanics were used to obtain information about self-reported race and ethnicity. Using NHANES, we categorized the participants into four racial and ethnic groups: Mexican Americans, non-Hispanic Black, non-Hispanic White, and other races. There are three levels of educational attainment: below high school, high school, and college graduate or greater. We classified household income into the following three levels based on the household PIR: low-income (≤1.3), moderate-income (1.3–3.5), and high-income (>3.5) using data used by US government agencies to report NHANES nutrition and health data.[70] BMI was calculated by dividing each participant's weight by their height's square (kg/m^2). According to the activity intensity within a week, work and recreational activities are divided into three levels: vigorous, moderate, and none or low.[71] Three categories of smoking status were used: never smoked (or smoked less than 100 cigarettes), past smokers (smoked at least 100 cigarettes but ceased smoking), and current smokers. The survey question "Have you had at least 12 drinks of any type of alcoholic beverage in any 1 year?" was employed to assess people's drinking status. Those who responded "yes" were classified as drinkers. The question "Have you been told by a doctor or health professional that you have ___?" was used to address hypertension, diabetes, stroke, CHD, and CHF. Participants' blood samples were sent to a remote lab for analysis and testing for TC, HDL, and GHb.

Statistical analysis

We considered complex sampling designs and weights following the NHANES analysis guidelines.[72] We used the sNfL subsample 2-year weight (WTSSNH2Y) as the sample weight for the research because it is present in the corresponding component of the NHANES.[32] Means (standard deviation, SD) for continuous variables and percentage frequencies for categorical variables were used to describe participant characteristics. T-tests (for continuous variables) and chi-squared tests (for categorical variables) were used to compare baseline characteristics between groups classified by ln(sNfL) quintiles. Specifically, because the sNfL levels were skewed, we transformed them using a natural logarithm to ensure they followed a normal distribution.

β and 95% CIs for the four cognitive tests with ln (sNfL) levels were calculated using weighted linear regression models. We used both unadjusted and multivariate-adjusted models to analyze the data separately. Without making any covariate adjustments, Model 1 was the crude model. Model 2 was modified to account for sociodemographic factors, work, and recreational activities. Model 3 is a fully adjusted model with all of the included covariates. Furthermore, restricted cubic spline (RCS) regression was carried out using four knots at the 5th, 35th, 65th, and 95th percentiles of ln(sNfL) levels to test the nonlinear relationship between ln(sNfL) concentrations and the four cognitive tests after adjusting all covariables in Model 3. After that, we used weighted segmented linear regression to conduct additional inflection point analyses. We also used stratified analysis to investigate further the association between ln(sNfL) and these tests in several population subgroups, including age, gender, race,

education level, family income, work activity, recreational activity, BMI, hypertension, diabetes, smoking status, and drinking subgroups. To test the robustness of our findings, we removed participants from the sensitivity analysis if their ln(sNfL) was less than 4.489 pg/mL (outliers were identified using the box plot approach).

STATA version 16 (StataCorp LP, College Station, Texas, USA), R software (version 4.2.1), and Free statistical software (version 1.7.1, FreeClinical Medical Technology Co., Ltd, Beijing, China) were used for all analyses. The threshold for statistical significance was a two-sided p value of 0.05. In particular, to address the issue of multiple comparisons in subgroup analysis, we implemented a Bonferroni adjustment to the significance threshold. This adjustment led to a more stringent entry aimed at controlling the family-wise error rate. Please refer to the attached materials for further information on the statistical analysis plan.

Results

Population characteristics

According to the quintiles of their ln(sNfL) levels, Table 1 demonstrates the baseline characteristics of all subjects. The individuals' mean ages, BMI, TCs, HDLs, GHbs, IRTs, DRTs, AFTs, and DSSTs were 66.31 (4.19) years, 29.37 (6.98) kg/m^2, 192.36 (42.25) mg/dL, 56.69 (17.70) mg/dL, 5.96 (1.04) %, 21.33 (4.05), 6.95 (2.06), 18.65 (5.66), and 54.03 (16.32), per the weighted analysis. Men made up 47.73% of the participants, who were essentially between the ages of 60 and 69 (73.86%) during the period of the NHANES examination. The distribution of the number of participants and levels of continuous covariates remained consistent among categories except for age, TC, GHb, and the four cognitive tests. Specifically, participants with ln(sNfL) levels in the range of 3.08–3.48 pg/mL (in the fourth quintile) were slightly older. In contrast, those with relatively high TC and GHb levels exhibited ln(sNfL) values that fell into the second (2.58–2.81 pg/mL) and fifth quintiles (3.49–6.21 pg/mL), respectively. In addition, participants with ln(sNfL) levels in the 2.58 to 2.81 pg/mL (in the second quintile) performed relatively well on all cognitive tests.

Association between sNfL levels and cognitive function

Table 2 shows the outcomes of the multiple linear regression using sample weights. In Models 1–3, the levels of ln (sNfL) and the four cognitive tests showed a negative relationship. In the crude model, the βs (95% CIs) for IRT, DRT, AFT, and DSST were −1.046 (−1.686 to −0.405), −0.424 (−0.770 to −0.077), −2.014 (−3.778 to −0.250), and −6.265 (−10.208 to −2.321). After adjusting for all confounders, the corresponding effect sizes (95% CIs) were −0.763 (−1.301 to −0.224), −0.308 (−0.576 to −0.04), −1.616 (−2.639 to −0.594), and −2.790 (−4.369 to −1.21), respectively. Furthermore, we employed RCS to model and visualize the relationship between predicted ln(sNfL) and βs of the four cognitive tests in Figure S1. After adjusting for all covariates, there was a nonlinear relationship between ln(sNfL) and DRT (p for nonlinearity = 0.002) and AFT (p for nonlinearity = 0.024), respectively, with an inflection point at approximately 2.7 pg/mL. In Table 3, segmented linear regression analysis suggested a significant negative correlation between ln(sNfL) and DRT (β (95% CI):-0.543 (−1.059 to −0.027)) and AFT (β (95% CI): −1.748 (−3.003 to −0.493)) when ln(sNfL) level was greater than 2.7 pg/mL.

Stratified analysis

Figure S2 presents the result of the stratified analysis for the fully adjusted model under sample-weighted investigation. Participants who engaged in no or little work (β (95% CI): −1.117 (−2.026 to −0.208)) and moderate recreational (β (95% CI): −1.519 (−2.561 to −0.477)) activity did not have diabetes (β (95% CI): −1.129 (−1.996 to −0.262)) showed a negative connection between ln(sNfL) and IRT. Only participants who did not have hypertension (β (95% CI): −0.946 (−1.756 to −0.136)) showed this negative correlation for DRT. Non-Hispanic white (β (95% CI): −1.684 (−2.85 to −0.518)) women (β (95% CI): −2.326 (−3.537 to −1.114)) aged 60–69 years (β (95% CI): −1.571 (−2.636 to −0.507)) with a college education (β (95% CI): −2.176 (−3.471 to −0.881)), overweight (β (95% CI): −3.224 (−4.619 to −1.829)), no or little work (β (95% CI): −2.025 (−3.301 to −0.749)), and recreational (β (95% CI): −1.955 (−3.428 to −0.481)) activity, hypertension (β (95% CI): −2.056 (−3.231 to −0.881)) as well as no diabetes (β (95% CI): −1.959 (−3.077 to −0.842)), frequently drank alcohol (β (95% CI): −1.574 (−2.732 to −0.415)) turned to have this negative association with AFT. Participants who were at least 70 years old (β (95% CI): −5.282 (−9.857 to −0.708)), overweight (β (95% CI): −4.282 (−8.076 to −0.489)) with hypertension (β (95% CI): −4.374 (−7.353 to −1.395)), did not have diabetes (β (95% CI): −3.793 (−6.913 to −0.674)), showed this negative association with the DSST. In addition, we discovered an inverse interaction between diabetes and ln(sNfL) levels for IRT (p for interaction = 0.021) and AFT (p for interaction = 0.037) (for details, see Tables S1–S4).

Table 1. Characteristics of participants in the NHANES 2013–2014 cycles.

	ln (sNfL), pg/mL						
Characteristic	Total 446	Q1 (1.96–2.57) 89	Q2 (2.58–2.81) 85	Q3 (2.82–3.07) 94	Q4 (3.08–3.48) 88	Q5 (3.49–6.21) 90	*p*-value
Age (years), mean (SD)	66.31 (4.19)	64.52 (3.60)	66.04 (3.51)	66.06 (4.30)	68.19 (4.29)	66.76 (4.47)	0.001*
Age (years), *n* (%)							0.038*
60–69	315 (73.86)	78 (87.85)	66 (82.41)	67 (71.48)	47 (57.93)	57 (68.65)	
≥70	131 (26.14)	11 (12.15)	19 (17.59)	27 (28.52)	41 (42.07)	33 (31.35)	
Gender, *n* (%)							0.537
Male	208 (47.73)	43 (50.97)	32 (44.6)	43 (39.55)	44 (53.49)	46 (50.22)	
Female	238 (52.27)	46 (49.03)	53 (55.4)	51 (60.45)	44 (46.51)	44 (49.78)	
Race, *n* (%)							0.292
Mexican American	47 (3.81)	14 (5.55)	8 (3.09)	9 (3.73)	7 (3.1)	9 (3.64)	
Non-Hispanic White	220 (78.9)	32 (73.9)	51 (86.59)	45 (77.24)	43 (75.79)	49 (80.03)	
Non-Hispanic Black	88 (9.02)	19 (10.76)	8 (3.79)	21 (10.41)	19 (10.06)	21 (10.64)	
Other race	91 (8.28)	24 (9.78)	18 (6.53)	19 (8.62)	19 (11.05)	11 (5.69)	
Education level, *n* (%)							0.193
Below high school	98 (13.8)	18 (13.2)	18 (13.01)	18 (13.21)	25 (15.73)	19 (13.93)	
High school	102 (20.24)	18 (11.1)	13 (15.21)	30 (34.31)	19 (20.25)	22 (21.13)	
College educated	246 (65.96)	53 (75.7)	54 (71.78)	46 (52.48)	44 (64.02)	49 (64.93)	
Family income, *n* (%)							0.213
Low income	129 (16.34)	23 (14.76)	22 (11.87)	27 (19.89)	27 (14.46)	30 (21.2)	
Medium income	170 (37.62)	32 (28.16)	33 (39.7)	35 (31.14)	31 (41.1)	39 (47.48)	
High income	147 (46.04)	34 (57.08)	30 (48.43)	32 (48.96)	30 (44.44)	21 (31.32)	
Work activity, *n* (%)							0.507
Vigorous	58 (16.23)	10 (16.89)	15 (17.13)	12 (20.29)	7 (8.47)	14 (18.27)	
Moderate	88 (20.4)	20 (25.77)	17 (19.95)	17 (21.26)	20 (23.59)	14 (11.65)	
No or lower	300 (63.37)	59 (57.34)	53 (62.92)	65 (58.45)	61 (67.94)	62 (70.09)	
Recreational activity, *n* (%)							0.143
Vigorous	67 (14.66)	12 (13.89)	17 (20.47)	14 (15.61)	9 (14.15)	15 (8.63)	
Moderate	139 (31.56)	34 (42.52)	19 (23.25)	33 (39.23)	32 (31.94)	21 (22.09)	
No or lower	240 (53.78)	43 (43.6)	49 (56.27)	47 (45.16)	47 (53.91)	54 (69.28)	
BMI, kg/m^2, mean (SD)	29.37 (6.98)	30.39 (7.46)	28.06 (4.99)	29.23 (6.45)	28.90 (8.72)	30.38 (6.76)	0.297
BMI, *n* (%)							0.069
Underweight	6 (1.75)	0	0	2 (1)	3 (7.61)	1 (0.35)	
Normal	115 (25.84)	21 (24.78)	28 (33.16)	20 (22.91)	23 (27.04)	23 (20.54)	
Overweight	159 (35.37)	32 (33.07)	30 (39.7)	38 (41.1)	32 (29.62)	27 (32.97)	
Obese	166 (37.04)	36 (42.14)	27 (27.13)	34 (34.99)	30 (35.73)	39 (46.14)	
Hypertension, *n* (%)							0.507
No	174 (44.93)	34 (43.81)	36 (45.68)	43 (54.53)	36 (45.34)	25 (35.55)	
Yes	272 (55.07)	55 (56.19)	49 (54.32)	51 (45.47)	52 (54.66)	65 (64.45)	
Diabetes, *n* (%)							0.052
No	349 (82.18)	75 (85.38)	75 (90.45)	73 (84.84)	62 (75.9)	64 (73.57)	
Yes	97 (17.82)	14 (14.62)	10 (9.55)	21 (15.16)	26 (24.1)	26 (26.43)	
Stroke, *n* (%)							0.584
No	422 (93.73)	88 (96.21)	79 (94.17)	90 (95.26)	80 (89.96)	85 (93.01)	
Yes	24 (6.27)	1 (3.79)	6 (5.83)	4 (4.74)	8 (10.04)	5 (6.99)	
CHF, *n* (%)							0.369
No	416 (93.1)	86 (93.35)	80 (95.3)	88 (96.02)	82 (94.03)	80 (86.71)	
Yes	30 (6.9)	3 (6.65)	5 (4.7)	6 (3.98)	6 (5.97)	10 (13.29)	
CHD, *n* (%)							0.114
No	407 (90.18)	83 (88.99)	84 (99.26)	82 (89)	79 (90.39)	79 (82.33)	
Yes	39 (9.82)	6 (11.01)	1 (0.74)	12 (11)	9 (9.61)	11 (17.67)	
Smoking status, *n* (%)							0.583
Never smoker	220 (49.41)	48 (52.08)	46 (53.2)	45 (47.4)	43 (51.46)	38 (42.58)	
Former smoker	165 (39.79)	38 (45.15)	30 (37.4)	33 (41.21)	28 (33.36)	36 (42.04)	
Current smoker	61 (10.8)	3 (2.78)	9 (9.4)	16 (11.38)	17 (15.18)	16 (15.38)	

(*Continued*)

Table 1 Continued.

	ln (sNfL), pg/mL						
Characteristic	Total 446	Q1 (1.96–2.57) 89	Q2 (2.58–2.81) 85	Q3 (2.82–3.07) 94	Q4 (3.08–3.48) 88	Q5 (3.49–6.21) 90	*p*-value
Drinking, *n* (%)							0.628
No	132 (26.23)	29 (28.55)	21 (22.95)	30 (31.23)	24 (20.04)	28 (28.77)	
Yes	314 (73.77)	60 (71.45)	64 (77.05)	64 (68.77)	64 (79.96)	62 (71.23)	
TC, mg/dL, mean (SD)	192.36 (42.25)	199.22 (40.16)	200.39 (39.96)	188.28 (45.80)	184.76 (45.42)	188.20 (38.18)	0.021*
HDL, mg/dL, mean (SD)	56.69 (17.70)	55.43 (15.07)	56.84 (16.82)	57.99 (15.69)	57.85 (21.33)	55.34 (19.08)	0.693
GHb, %, mean (SD)	5.96 (1.04)	5.76 (0.62)	5.76 (0.84)	5.96 (0.67)	6.12 (1.22)	6.20 (1.52)	0.010*
IRT, mean (SD)	21.33 (4.05)	22.19 (3.12)	22.12 (3.76)	21.46 (3.91)	20.09 (4.78)	20.74 (4.18)	0.006*
DRT, mean (SD)	6.95 (2.06)	7.17 (1.97)	7.45 (1.68)	7.03 (2.32)	6.63 (2.16)	6.44 (2.01)	0.004*
AFT, mean (SD)	18.65 (5.66)	19.43 (5.27)	20.82 (6.05)	18.72 (5.58)	16.96 (5.72)	17.10 (4.68)	0.035*
DSST, mean (SD)	54.03 (16.32)	57.86 (14.33)	58.80 (17.26)	53.96 (15.57)	50.29 (15.35)	48.78 (16.61)	0.007*

Abbreviations: AFT, animal fluency test; BMI, body mass index; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; DRT, delayed recall test; DSST, digit symbol substitution test; GHb, glycated hemoglobin; HDL, high-density lipoprotein; IRT, immediate recall test; NHANES, National Health and Nutrition Examination Survey; Q, quartiles; SD, standard deviation; sNfL, serum neurofilament light; TC, total cholesterol.
*$p < 0.05$.

Table 2. Association between serum neurofilament light and four cognitive tests.

	Model 1		Model 2		Model 3	
Cognitive tests	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
IRT	−1.046 (−1.686 to −0.405)	0.003*	−0.802 (−1.347 to −0.257)	0.007*	−0.763 (−1.301 to −0.224)	0.009*
DRT	−0.424 (−0.770 to −0.077)	0.020*	−0.349 (−0.661 to −0.037)	0.031*	−0.308 (−0.576 to −0.04)	0.027*
AFT	−2.014 (−3.778 to −0.250)	0.028*	−1.592 (−2.732 to −0.452)	0.009*	−1.616 (−2.639 to −0.594)	0.004*
DSST	−6.265 (−10.208 to −2.321)	0.004*	−3.441 (−5.097 to −1.786)	<0.001	−2.790 (−4.369 to −1.21)	0.002*

Model 1: Crude model. Model 2: Adjusted with age, gender, race, education level, family income, work activity, and recreational activity. Model 3: Adjusted with age, gender, race, education level, family income, work activity, recreational activity, BMI, hypertension, diabetes, congestive heart failure, coronary heart disease, stroke, smoking status, drinking, glycated hemoglobin, total cholesterol, and high-density lipoprotein.
Abbreviations: AFT, animal fluency test; CI, confidence interval; DSST, digit symbol substitution test; IRT, immediate recall test; DRT, delayed recall test.
*$p < 0.05$.

Sensitivity analyses

After excluding individuals with extreme ln(sNfL), there was still a negative correlation between the serum neurofilament light chain and most cognitive test scores. Ln (sNfL) levels were still negatively associated with IRT (β (95% CI): −0.894 (−1.76 to −0.027)), DRT (β (95% CI): −0.476 (−0.921 to −0.031)), and AFT (β (95% CI): −2.031 (−2.882 to −1.179)) in the fully adjusted model, respectively, except for DSST (for details, see Table S5).

Discussion

This cross-sectional research involving an older US population found a negative correlation between sNfL levels and cognitive performance. Further analysis revealed a nonlinear relationship between ln(sNfL) levels and DRT and AFT, respectively, with an inflection point value of around 2.7 pg/mL. Stratified analysis suggested that for different kinds of cognitive tests, the negative correlation between the levels of ln(sNfL) and them was reflected in specific subgroups with various characteristics. Moreover, for IRT and AFT, there was an inverse interaction between diabetes and ln(sNfL).

Previous research has also found a negative correlation between the levels of NfL and cognitive function. A scoping review that included 37 original studies found that higher levels of NfL (sample sources including serum, plasma, or cerebrospinal fluid) were associated with poorer cognitive performance in many neurological diseases such as AD, Huntington's disease, multiple sclerosis, Parkinson's disease, and traumatic brain injury.[73] In

Table 3. Segmented linear regression analysis of the relationship between serum neurofilament light and cognitive performance.

	Model 3	
Cognitive tests	β (95% CI)	*p*-value
DRT		
ln(sNfL) < 2.7 pg/mL	1.377 (−1.521 to 4.274)	0.351
ln(sNfL) ≥2.7 pg/mL	−0.543 (−1.059 to −0.027)	0.039*
AFT		
ln(sNfL) < 2.7 pg/mL	3.671 (−3.073 to 10.415)	0.285
ln(sNfL) ≥2.7 pg/mL	−1.748 (−3.003 to −0.493)	0.006*

Model 3: Adjusted with age, gender, race, education level, family income, work activity, recreational activity, BMI, hypertension, diabetes, congestive heart failure, coronary heart disease, stroke, smoking status, drinking, glycated hemoglobin, total cholesterol, and high-density lipoprotein.

Abbreviations: AFT, animal fluency test; CI, confidence interval; DRT, delayed recall test.

*$p < 0.05$.

another meta-analysis of biological markers for AD, researchers found that the increase in cerebrospinal fluid NfL was more pronounced in the AD group compared to the control group (cognitively normal), with a combined effect size (95% CI) of 2.35 (1.90–2.91).[74] However, cerebrospinal fluid collection is an invasive procedure[75] and is challenging to perform for screening in the general population. Therefore, studying NfL levels in blood samples as a biological marker for diagnosing cognitive decline has more excellent research value. A study conducted on a population of Latino older adults[21] found that plasma NfL levels were negatively correlated with neurodegeneration-related imaging biomarkers such as "meta ROI" ($\beta = -0.023$, $p = 0.014$), mean thickness of the temporal subregion ($\beta = -0.022$, $p = 0.009$), mean thickness of the middle temporal gyrus ($\beta = -0.033$, $p < 0.001$), and mean thickness of the cingulate gyrus ($\beta = -0.017$, $p = 0.040$) while being positively correlated with overall brain amyloid load ($\beta = 0.004$, $p = 0.02$).

Additionally, in a cohort study involving 625 middle-aged participants, Beydoun et al. found that baseline plasma NfL levels were associated with rapid cognitive decline in White individuals or those over 50 years old, and the rate of plasma NfL increase was related to a rapid decline in verbal fluency in males.[76] Another longitudinal study in AD patients found a significant correlation between dynamic changes in serum NfL and cognitive decline, and compared to cross-sectional analysis, this change could identify patients carrying AD genes a decade earlier. However, due to sample size and time limitations, the study cannot yet be applied to clinical predictions.[77] Another cohort study involving 335 normal individuals revealed a negative correlation between the annual changes in mini-mental state examination (MMSE) scores over time and initial serum NfL levels ($r_s = -0.273$, $p < 0.01$).[78]

Furthermore, another cohort study found that the high sNfL group had a higher risk of substantial cognitive impairment change (i.e., transitioning from normal to mild cognitive impairment (MCI) or from MCI to dementia) (log-rank test $p < 0.001$). Elevated sNfL levels in the MCI population served as an independent predictor of significant cognitive impairment change (multivariable Cox regression model analysis: HR [95% CI] 13.640 [1.346–138.270]).[24] Our research confirms the above study's finding that a negative correlation exists between ln(sNfL) levels and cognition. Moreover, the data utilized in our study used a complex sampling method to represent the US elderly population for correlation analysis, enhancing its generalizability. In addition, few studies have analyzed the dose–response relationship between sNfL levels and cognitive decline. Our study, based on RCS regression, found a nonlinear relationship between ln(sNfL) levels and DRT and AFT. Only when ln(sNfL) levels were greater than or equal to 2.7 pg/mL did DRT and AFT scores significantly decrease with increasing ln(sNfL) levels. This analysis suggests that sNfL, a central nervous system damage biomarker, demonstrates a threshold effect in its relationship with DRT and AFT. Nevertheless, it is worth noting that the context of the other two cognitive tests did not observe such a nonlinear relationship. Therefore, additional research is warranted to determine whether this inflection point value holds diagnostic significance.

In addition, our stratified analysis results showed that sNfL levels were only associated with cognitive function in subgroups of individuals with specific characteristics by different cognitive tests. To our knowledge, few previous research addressed this issue. A study involving 503 non-Hispanic White and 357 Mexican American participants found that plasma NfL levels were associated with poorer verbal fluency (AFT scores) in non-Hispanic Whites, regardless of cognitive impairment,[79] consistent with our findings. However, in another study, Beydoun et al. found that the rate of the annual increase in plasma NfL levels was associated with a decline in verbal fluency in males. Among participants with higher economic status, the speed of the yearly rise in plasma NfL levels was associated with a slower loss in verbal fluency.[76] Nevertheless, it is worth noting that the participants in that study were middle-aged individuals with an average age range of 30–66 years.

Furthermore, our study also revealed an inverse interaction between sNfL levels and diabetes in the IRT and AFT tests, suggesting a possible positive association between them. And a few previous studies reported similar findings. Ciardullo et al. found that diabetes patients had higher sNfL levels than nondiabetic participants in each age

group, and multivariable linear regression suggested a positive relationship between ln(sNfL) levels and diabetes.[37] Additionally, Thota et al. found that plasma NfL levels were higher in individuals with Type 2 diabetes and prediabetes than in those with normal blood glucose levels.[80] Furthermore, Fitzgerald et al.'s study[36] also identified a significant correlation between diabetes and elevated sNfL levels.

Although the biological mechanisms underlying the relationship between elevated sNfL levels and cognitive decline are not yet fully understood, we can speculate that the following reasons may contribute to this association based on existing evidence. First, as a structural protein widely distributed in neuronal axons, Neurofilaments are primarily involved in maintaining the stability of the cytoskeleton.[81,82] Among the four subunits of Neurofilaments, NfL is the most abundant and soluble, making it the most easily detectable subunit of Neurofilaments.[83] When axonal damage occurs, NfL is released into the extracellular fluid and can be detected in cerebrospinal fluid or peripheral blood.[84] Theoretically, any disease that causes neuronal and axonal damage (including neurodegenerative diseases like AD) significantly increases NfL levels.[85] Second, studies have shown that the integrity of axons plays a crucial role in maintaining cognitive function.[86] Similarly, axonal degeneration is an essential feature of neurodegenerative diseases and an important factor contributing to cognitive impairment.[87,88] Therefore, neurodegenerative diseases are often associated with elevated peripheral blood NfL levels.[89,90] In addition, two genetic studies have found significant associations between specific single-nucleotide polymorphisms related to the high risk of AD and increased NfL levels,[91,92] suggesting that NfL may be involved in cognitive impairment through genetic mechanisms. However, to elucidate the relationship between sNfL and cognitive function, further basic experiments and clinically rigorous studies with high levels of evidence are needed for exploration.

Nevertheless, our study has some limitations. First, despite controlling for confounding factors through various methods, such as multivariable regression and stratified analysis, we could not eliminate residual confounding effects from unmeasured factors. Unmeasured confounding factors could introduce bias into the correlation analysis between sNfL and cognitive tests. Nonetheless, we have diligently eliminated known major confounding factors through a comprehensive literature review,[55–69] ensuring the reliability of our analytical results. Second, although our study utilized a thorough assessment of cognitive function through four representative tests, caution should be exercised when interpreting effect sizes, as there is currently a lack of standard gold quantification for defining cognitive impairment. Cognitive test scores capture only certain aspects of cognitive performance excellence.[49,93] In the future, we plan to conduct relevant analyses using techniques that facilitate a more comprehensive assessment of cognitive functioning, potentially enhancing our ability to gauge clinical relevance. Third, due to the inherent nature of cross-sectional studies, we cannot make causal inferences regarding the relationship between sNfL levels and cognitive function. To further establish this association, future longitudinal research is required. Lastly, despite NHANES employing a complex multi-stage probability sampling method to reduce population selection bias, our study utilized a relatively small unweighted sample size. Consequently, caution should be taken while interpreting the findings, particularly regarding population representativeness and analysis outcomes within specific subgroups with limited sample sizes. If new cycle-related data become available in the database, we intend to incorporate and combine it in future research to enhance its representativeness.

In summary, our study found a negative association between ln(sNfL) levels and cognitive function in the overall elderly population in the United States, with a nonlinear relationship observed in delayed memory and language fluency tests. This finding suggests that sNfL may serve as a potential biological marker for monitoring cognitive decline and enabling early intervention in high-risk populations at risk of developing AD. These results will need to be confirmed by more longitudinal research.

Author Contributions

Xiaodong Liu: conceptualization; data collection; formal analysis; methodology; writing—original draft; writing—review and editing. Jun Chen: supervision; writing—review and editing. Chen Meng: data collection; writing—review and editing. Lan Zhou: data collection; writing—review and editing. Yong Liu: data collection; writing—review and editing.

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Conflict of Interest

The study's authors affirm that no financial or commercial ties might be viewed as having a potential conflict of interest.

Ethical Statement

The study was carried out in accordance with the Declaration of Helsinki. And we used publicly available data to carry out this research. Therefore, approval from the institutional review board was not necessary.

Data Availability Statement

Online resources are provided for this study's publicly accessible datasets. The name of the repository or repositories and its accession numbers can be found online at http://www.cdc.gov/nchs/nhanes.htm (Accessed 29 Jun 2023).

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1
Figure S2
Appendix S1

